Revision

2250 9946

Pharmacology :

It's the science (study, Knowledge) of drugs & their effect on human body.
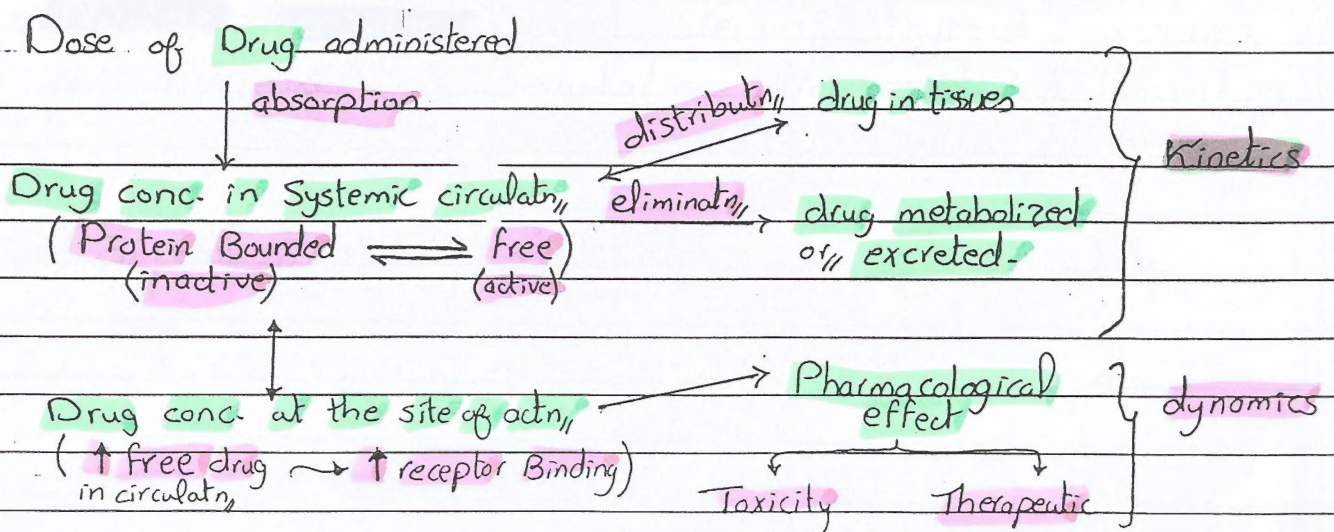
Pharmacodynamics :

It studies the effect of drug on living systems (human body). , Biochemichal , physiological conditions that affects the drug, M.O.A.

Pharmacokinetics :

It studies the action of body on drug including absorptₙ , distributₙ, Metabolism, excretion (ADME)

Nice sketch

Dose of Drug administered
| absorption

→ distributₙ drug in tisues

Drug conc. in Systemic circulatₙ ← eliminatₙ → drug metabolized
(Protein Bounded ⇌ free)   ०⁄⁄ excreted.
(inactive)   (active)

Drug conc. at the site of actₙ → Pharmacological effect
(↑free drug ⤳ ↑receptor Binding)
in circulatₙ   ↓
                        Toxicity   Therapeutic

} Kinetics

} dynomics

(*) Drug molecules interact é a special molecule in the Biological system that a regulatory role this Molecule is called "Receptors"

(*) Not all drugs act by receptor Binding such as :
① antacids
② Charcoal tabs ⟿ adsorption of intestinal gases
③ Laxatives , diuretics

Receptor types :

① Agonist (Ligand) gated channels ⟿ made up of proteins Subunits forming central pore
examples : nicotinic & GABA receptors , glutamate

② G-protein coupled receptors ⟿ Form 2nd messenger.
muscarinic R - norAdrenergic R - Dopamenergic R

③ Kinase - Linked surface receptors ⟿ include receptors For insulin

④ Nuclear receptors for steroid, thyroid hormones in nucleus ⟿ regulating transcription & translation.
insulin. Histamine

page ⑩ مكسن نجيب N sketch في الطورة الطريقة السابقة
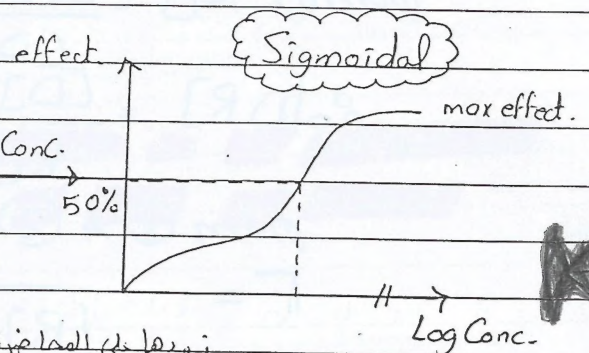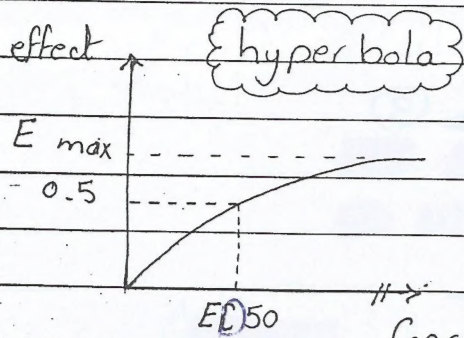
وبراحة اما النزم نجزئ ال ونسسنى شوية

Pharmacodynamics :

طريقة تأثير

It's the study of relation between conc. of drug * & the response produced   at the receptor.

* **Magnitude** of response is proportional to the no. of **Complexes** (Drug - receptor)
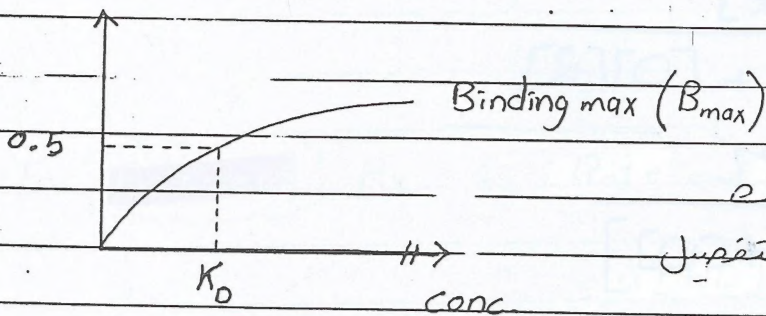→ This is called (occupation theory or Key & Lock)

effect ↑ {hyperbola}

E_{max}

— 0.5

EC_{50} → Conc. (at receptor site) ويرجع في المحاضرة السابقة (مهم)

Dose which give 50% response

Drug المحاضرة من طبعًا هو 2 curves الو

effect ↑ {Sigmoidal}

taking Log Conc.

max effect.

50%

→ Log Conc.

receptor bound drug   أما الصورة

Binding max (B_{max})

0.5

K_0 → conc.

هذه الـ curve هي فرق حاجة ومتشبه مع العلاقة اللوغاريتمية بالتفصيل العمل مع الـ لقاء

$$* [D] + [R] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [DR] \longrightarrow \text{Response}$$
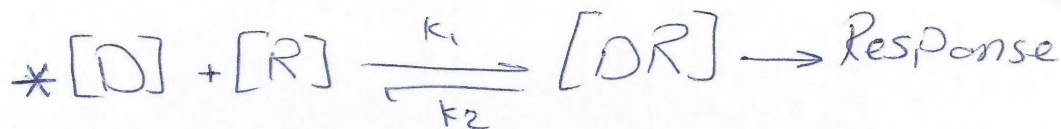
Forward Rx $\quad \text{Rate}_1 = \dfrac{d[RD]}{dt} = k_1 [D][R]$ $\longrightarrow$ associat^n const.

Backward Rx $\quad \text{Rate}_2 = -\dfrac{d[DR]}{dt} = k_2 [DR]$ $\longrightarrow$ dissociat^n $\sim$

$$\therefore \text{At equilibrium } \text{Rate}_1 = \text{Rate}_2$$
$$\therefore k_1 [D][R] = k_2 [DR]$$

associat^n $\leftarrow$ $\dfrac{k_2}{k_1} = \dfrac{[D][R]}{[DR]} = k_D$ $\rightarrow$ equilibrium distribut^n Const. $\longrightarrow$ ①
Rate Const. $\qquad\qquad\qquad\qquad\qquad$ Dissociat^n

Fractional $\leftarrow f = \dfrac{[DR] \text{ complexes}}{[R]_{free} + [DR] \text{ complexes}}$ $\longrightarrow$ ②
occupancy

from ① $\quad k_D = \dfrac{[D][R]}{[DR]}$

$$\therefore [DR] = \dfrac{[D][R]}{k_D} \quad \longrightarrow ③$$

from ③ & ②

$$F = \dfrac{\dfrac{[D][R]}{k_D}}{[R] + \dfrac{[D][R]}{k_D}}$$

$$F = \dfrac{[D][R]}{k_D \left[[R] + \dfrac{[D][R]}{k_D} \right]}$$

$$F = \dfrac{[D][R]}{k_D [R] + [D][R]}$$
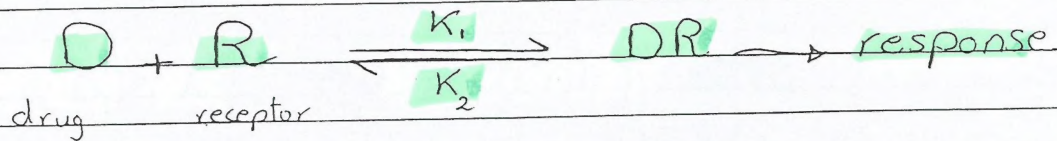
$$F = \dfrac{[D][R]}{[R][k_D * [D]]}$$

$$F = \dfrac{[D]}{[D] + k_D}$$

$$\boxed{\therefore F = \dfrac{[DR]}{[R] + [DR]} = \dfrac{[D]}{[D] + k_D}}$$

$\left| \begin{array}{l} \text{when } k_D = [D] \\ \therefore F = \dfrac{[D]}{2[D]} \\ \boxed{F = \dfrac{1}{2}} \end{array} \right.$

<u>i.e 1)Drug occupy 50% of Receptors</u>

كل اللي إحنا قلناه فى طبق زكام موجودة فى المطقة
السابقة ← تعالوا بنا نحل فى متطرقتنا

Binding Reaction

$$D + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DR \longrightarrow response$$

drug   receptor

Binding reaction follow (Law of Mass action) which
states that:

"The rate of chemical Rx is proportional
to the product of conc. of reactants."

∴ for (Forward) Rx : Rate $\sim \dfrac{d[RD]}{dt} \propto [D][R]$

∴ $\dfrac{d.[RD]}{dt} = const. [D][R]$

$\downarrow$

K_1

(association rate constant)

For (Backward) Rx : Rate $\sim -\dfrac{d[RD]}{dt} \propto [DR]$

∴ $-\dfrac{d[RD]}{dt} = const. [DR]$

-ve sign for backward Rx

$\downarrow$

K_2

(dissociation rate constant)

(*) (At Equilibrium :)   The 2 rates of Forward &
                          Backward Rx(s) are equal.

$$\therefore \frac{d[RD]}{dt} = -\frac{d[DR]}{dt}$$

$$\therefore K_1[D][R] = K_2[DR]$$

$$\therefore \frac{K_2}{K_1} = \frac{[D][R]}{[DR]} = K_D \quad \text{equilibrium dissociation constant.}$$

هي يعني
خلّيك عامل شي مهم ونفترض اللّا هو مهم ليا

إحنا بنتكلم عن كل ده شباب نعرف فكرة قلّة أهمية essential fractional occupancy

$$f_r = \frac{drug - receptor\ complexes}{total\ receptors}$$

fractional occupancy

يعني أنا أخذت drug معين مسكت بعض في receptors الـ
وعمل complexes وهناك بيبقى في receptors الـ free

إحنا بنقول في كمية الـ receptors اللي عملت complexes ومقسمة
الـ total receptors اللي هم أصلاً موجودة

$$\therefore f_r = \frac{[DR]\ complexes}{[R]_{free} + [DR]_{complexes}}$$

وتكتب القانون الأخير ده تاني علشانه مهم وهنشتغل عليه دلوقتي

$$f = \frac{[DR]}{[R] + [DR]} = \frac{[D]}{[D] + K_D}$$

Mathematical derivation نعمل اللي هو ده وده علشان نتأكد أن ال

We said that :

$$K_D = \frac{[R][D]}{[DR]}$$

$$\therefore \boxed{[DR] = \frac{[R][D]}{K_D}} \longrightarrow \text{①}$$

، We said that : $\boxed{f = \frac{[DR]}{[R] + [DR]}} \longrightarrow \text{②}$

→ By Substituting From ① in ②

$$\therefore f = \frac{\dfrac{[R] \times [D]}{K_D}}{[R] + \dfrac{[R] \times [D]}{K_D}} = \frac{[R] \times [D]}{K_D \left([R] + \dfrac{[R] \times [D]}{K_D}\right)}$$

$$= \frac{[R] \times [D]}{K_D[R] + [R][D]} = \frac{[R] \times [D]}{[R]\left(K_D + [D]\right)} = \frac{[D]}{K_D + [D]}$$

Q.E.D

والكلام ده زي ما قولنا Derivation ده ممكن يجي سؤال في الامتحان

∴ We finally proved that :

$$f_r = \frac{[DR]}{[R] + [DR]} = \frac{[D]}{[D] + K_D}$$

طيب و بعدين ← إنت عايز إيه يعني ايمتى هانطبقها .

(*) We can conclude that :

as [D] (drug dose) increases → $f_r \uparrow$ → so response $\uparrow$
, as K_D (equil. dissociat$_n$ const.) decrease → $f_r \uparrow$ → " " " "

ماشي ← إقتنعنا بال point ← بس ليش نختار قيمة K_D ثابتة ؟

(*) When [D] = K_D → the drug will occupy 50% of the total receptors present.

ie// $f_r = \frac{[D]}{[D] + K_D} = \frac{[D]}{[D] + [D]} = \frac{[D]}{2[D]} = \boxed{\frac{1}{2}}$

∴ Drug occupies $\frac{1}{2}$ (50%) of total receptors

ماشي ← و هاي ال Point في كلام مشكلة ؟

طيب ← بس هاي ال Point منين تجيب لينا تعريف ال K_D

علشان نجيب تعريف الـ K_D من نفسها بالعكس ← إزاي؟

يعني نقول لما نكون $f = \frac{1}{2}$ (50%) ← ده يبقى أكبر الـ K_D

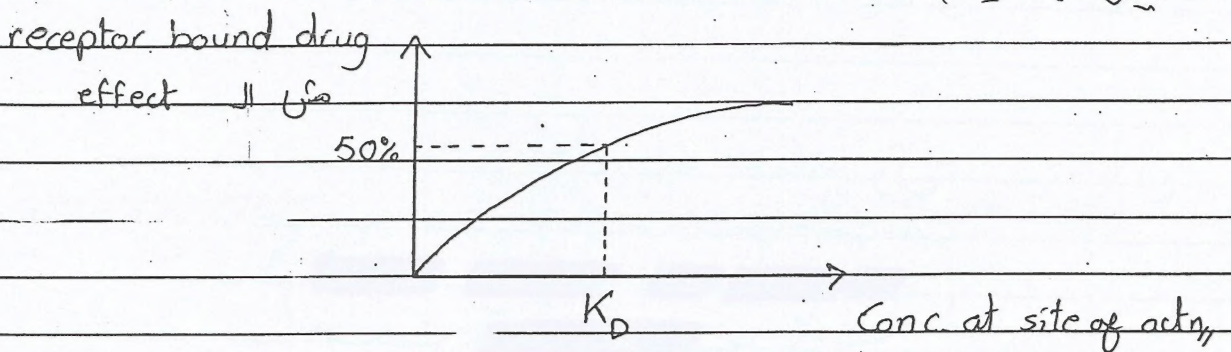مستوى الـ conc. بتاع الـ free drug (D)

صح و لا غلط أنا كمان؟

.: $K_D = [D]$ when $f = 50\%$

.: K_D (equilibrium dissociation const.) Can be defined as

"It's the conc. of free drug at which half of maximal receptor binding or, fractional occupancy is observed"

و من هنا ممكن نرجع الـ curve اللي قلنا إنا مهم وقلنا وشرحنا بالتفصيل يعني

receptor bound drug من الـ effect

وقلنا عليها مهم وخطط في محنا

طيب عايز نقول حاجة تانية عن الـ K_D؟

آه عايز حاجة من إقلاق المهمة

آخر حاجة مع الـ K_D

(⊗) K_D is a constant that characterizes the receptor **affinity** for binding the drug in a **Reciprocal fashion**

كدة يا بابا نستفيد ايه من الـ K_D ده
الفارغ ده ؟

→ This means that if K_D is ↑ فـ f is ↓
فـ surely this drug has low affinity to receptors
and Vice Versa . N.B K_D only have relation ē
Affinity **not** potency or efficacy

ie// affinity $\propto \dfrac{1}{K_D}$ as may be ↓ drug have ↑ affinity
but ē ↓ potency and efficacy .

وكده نبقى خلصنا الـ نقطة الخاصة بالـ equations ديّ اللي ظلمنا
و نتمنى انها تكون وصلت كويس
و لو هناك أي سؤال أو إستفسار مـ لاتتردد مـ تعالي واسأل

ولوقتي نقول حاجة جديدة

((**Forces Binding the drug to Receptors**))

They may be :
① Covalent bonds
or // ② ionic bonds
or // ③ H - bonds
or // ④ hydrophobic force (apolar)
or // ⑤ Van der Waal force (dipolar)

وحدة كلية صيدلة

Routes of Drug Administratn

A Enteral : → i.e. through the GIT

1) Oral : (as capsules, tablets)

- Most common, economical, safe.
- Most variable (differ according to physical characters, presence of food or other drugs, destruction by digestive enzymes or low gastric pH)

- Undergo first pass effect of portal circulation

- Villi of upper intestine provide an extremely large Surface area.

2) Sublingual : → drug is placed under the tongue

* Drug pass through cappillaries network to systemic circulation

* Avoid metabolism in liver (1st pass effect) or intestine.

3) Rectal :

* About 50% of drugs given rectally avoid liver metabolism. [first Pass effect]

* Useful in patients with vomiting or unconscious patients خاصةً عن الوعي

* Unreliable absorption →

علشان في 50% من الادوية ممكن نجيمع 1st pass effect في ال liver

* كده خلصنا اول route → معلش هو كاننا نظمس بس كله حاجات احنا عارفينها من قبل كده

تانت نوع 0000

B Parentral :

بقى امراية الدكتور اللي بيبى الحقنة

* disadv.: risk of infection, pain & local irritation

1) IV :

* Useful for poorly absorbed drugs that are soluble.

(soluble drug → i.e. ionized → ∴ not absorbed through the GIT (acts only on unionized drugs) but absorbed through IV injection)

* Avoid first pass metabolism through the liver

* 100% absorption & immediate response.

* Problem of overdose treatment

نجن لو اخذ الحياه جبرتة زيادة ← يلا السلامة ← مش هتفقه

2) IM: (Intramuscular)

* for aqueous drugs → rapid response.
  or oily ones → depot release

* Vol. < 5ml (c.c.)

3) Subcutaneous:

اقل خطورة
* It is slower and less hazardous than IV

examples: + epinephrine with local anaesthetics (to prolong their duration)

+ Insulin.

* ودول طبعاً استهر اتنين routes هنا من آحسن حاجة وهى تشكيلة من routes تانية ٥٥٥٥٥

C) Others:

1) Inhalation:

* For gaseous drugs (anaesthetics, antiasthmatics)

* Rapid onset of action.

2) Intranasal :

examples :

· Calcitonin hormone for osteoporosis
· Cocaine abuse   .. تعامل الكوكايـن

3) Intrathecal : → injection into the CSF

* example : Methotrexate in case of leukemia

4) Topical :   على الجلد مـن برة

as : Clotrimazole as antifungal (Local)

absorption   دى بس ما يحصلوش اى ← بس يشتغل من برة لما يشتغل

5) Transdermal :

as : Patches of nitroglycerin (systemic for ttt of angina)

كده خلصنا الجزء الشن ده ← نشوف جزء جديد فن المحاضرة
دى 0000

بس الاول عايزين تفتكـ سـوا الـ def. بتاح الـ

Pharmakokinetics 000

حد فاكـر ؟!!

* **Pharmakokinetics** : effect of body on drug

$$[ABME]$$

absoption ← ↓ ↘ → Excretion.

Distribution metabolism

دلــوقتي هنـشوف واحدة واحدة من دول بالتفصيل الممل ٥٥٥٥
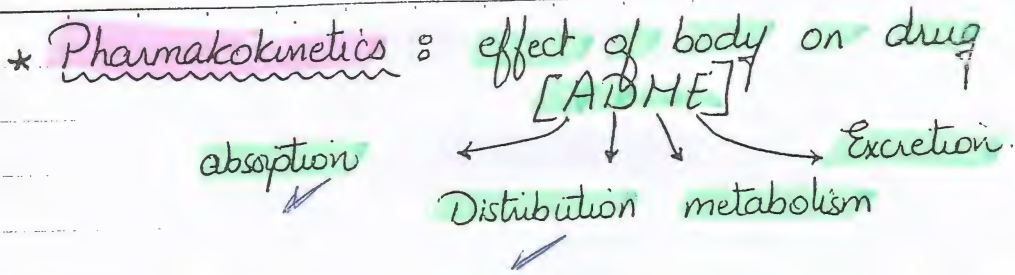
7 Absorption

* **Definition** :

It is the transfer of drug from the administration site to blood.

N.B : For drugs to traverse cellular barriers (eg: GIT mucosa) ⟶ these drugs have to cross the lipid membrane .

يعني الدواء هنلاقي عندي من الـ stomach وعايزاه يوصل للدم يبقي طبيعي لازم نيجي من خلال الـ GITmucosa يعني لازم يعرف يعبر من خلال الـ lipid memb.

طب هيعبر الـ memb. ازاي؟

* **Drugs cross lipid membranes mainly by** :

A Passive Diffusion :

depends on :

1) Conc. gradient (i.e. high → low conc)

2) Lipid solubility

* **Factors aff. Passive diffusion :**

↳ "Fick's Law"

a) Passive diffusion → directly prop. to SA of memb.
(tht's why upper intestine has very good absorption,
also using syringe of small SA needle has better
diffusion than one with large SA)

b) Passive diffusion → inversely prop to the thickness of
the memb.

(N.B:) Majority of drugs use this method.

③ **Active Transport :**

* ATP dependant (requires energy) ✓
* Against conc. gradient.
* Using specific carrier protein.

© **Facilitated diffusion:**

═══════════════ ↝ another carrier mediated
transport

* without energy

example: - Insulin senitive muscle cell glucose transporter
- P glycoprotein efflux transporter.

المكتوب جميع كل انواع الـ transport في الكبد الك جاى هـ ٥ ٥ ٥ ٥ ٥

Drug Transport across membranes

Mechanism	Energy	Carrier	Notes
Passive diff.	No	No	ماقالتش كتير ٥ ٥ ٥ قلبنا تقليب كام مرة و قالت الكتابة
Facilitated diff	No	Yes	
Aqueous channels	No	No	
Active transport	Yes	Yes	

• [Passive diffusion No Energy
 [Aqueous Channels No Carrier

• Active Transport Yes Energy
  Yes Carrier

• Facilated Channels No Energy
  Yes Carrier

* Effect of pH on drug absorption :

* Most drugs are either weak acids ($3 < pka < 7$) or weak bases.

* drugs cross membranes more readily if they are uncharged & more lipid soluble .

* **Dissociation constant (pKa):**
  _____ is the pH at which half of the drug is in ionized form.

* pKa is drug's acid dissociation constant.
* pKa is low for acids & high for bases (7 7)

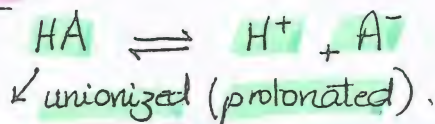* **To determine the uncharged absorbed portion of the drug:** _____

  خليك في الكلام الي فوق بس

  $pKa - pH$ stay from ...

  use "Handerson - Hasselbalch eqn".

$$pKa - pH = \log \frac{[protonated]}{[unprotonated]}$$

Weak acids:

$$HA \rightleftharpoons H^+ + A^-$$
↙ unionized (protonated).

Weak bases:

$$BH^+ \rightleftharpoons B + H^+$$
ionized (protonated)
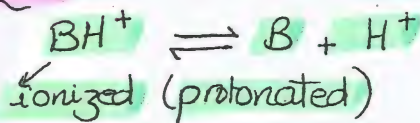
(N.B) protonated form = unionized acids , ionized bases

Weak acids	Weak base
$Pka - PH = \log \dfrac{un\,Ionized\ form}{Ionized\ form}$	$Pka - PH = \log \dfrac{Ionized\ form}{un\,Ionized\ ''}$
$HA \rightleftharpoons H^+ + A^-$	$BH^+ \rightleftharpoons H^+ + B$
↓ unIonized (Protonated)	↓ Protonated (Ionized)
• ↑pH → ↓H⁺ Rx forward → Ionized ↑absorptn	↓pH → ↑H⁺ Rx Backwork → Ionized → ↓absorptn

فى تعريف كده قاله الدكتور وهــوة
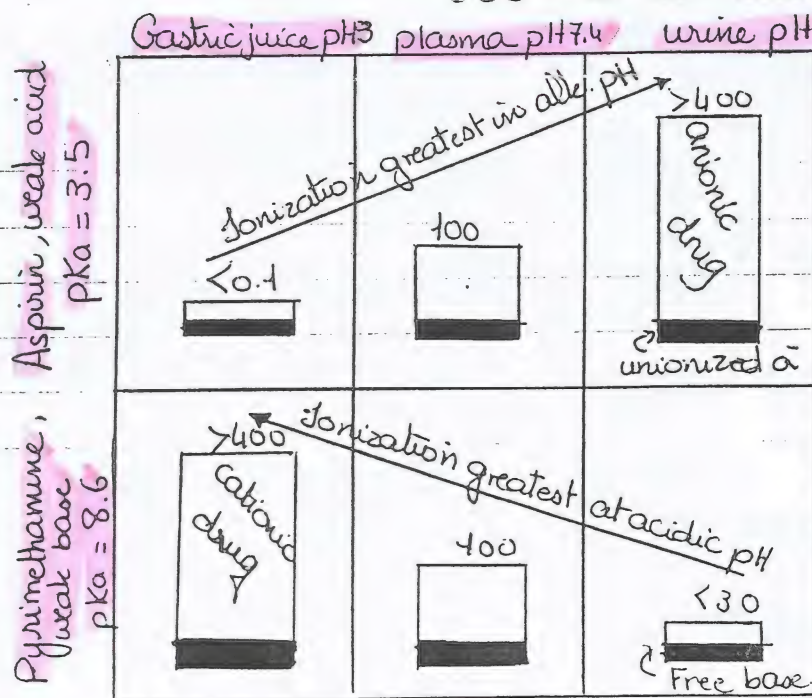
* pH partition (Ion trapping):

weak acids tend to accumulate in compartments of relatively high pH, while weak bases tend to accumulate in compartments of relatively low pH.

ودى منطق جداً لأن لو بصينا هناكلك على الـ eq؟ بتاعت الـ weak base
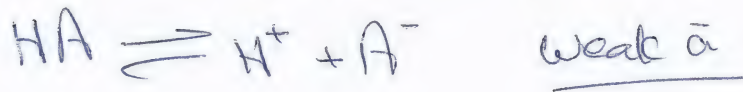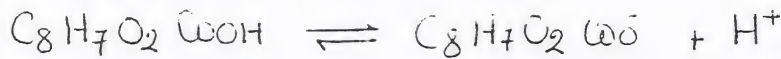
$$BH^+ \rightleftharpoons H^+ + B$$

فى الـ low pH ← هيكون عنى H^+ كتير اوى فالـ reaction ده هيمشى backward فى اتجاه الـ BH^+ الى هو الـ ionized form واحنا قلنا قبل كده ان الى بيحصله absorption هو الـ unionized form ← ده مش هيحصله abs. يبقى هيحصله abs. يبقى هيحصله trapping او accumulation.

ونفس الكلام مع الـ à weak بس بالعكس ٥٥٥٥

* طب تعالــوا نشـوف example ومسألتيـن خفاف كده عشان نفهم خاصية الكلام الى قلناه ده كله ٥٥٥

Gastric juice pH3   plasma pH7.4   urine pH8

Aspirin, weak acid pKa = 3.5

Ionization greatest in alky pH

Pyrimethamine, weak base pKa = 8.6

Ionization greatest at acidic pH

Aspirin:

$$C_8 H_7 O_2 \text{ COOH} \rightleftharpoons C_8 H_7 O_2 \text{ COO}^- + H^+$$

$$HA \rightleftharpoons H^+ + A^- \qquad \underline{weak\ \bar{a}}$$

Pyrimethamine:

$$C_{12} H_{12} Cl\ N_3\ NH_3^+ \rightleftharpoons C_{12}H_{11} Cl\ N_3 NH_2 + H^+$$

$$BH^+ \rightleftharpoons B + H^+ \qquad \underline{weak\ b}$$
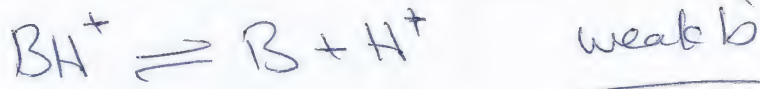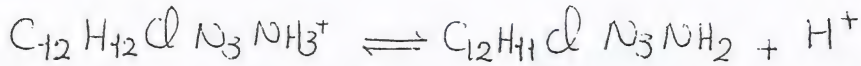
Problem:

Aspirin (pKa = 4) at stomach (pH 2) , will it be absorbed or not ?!

هنعوّض ببساطة فى ال eq؟ وينشوف نسبة ال protonated : unprotonated وبما ان ال aspirin دى weak acid بيبقى ال protonated = unionized والـ unionized بيحصل abs. احسن يبقى مفروض الآتى هنعرف كيف تعالوا !؟ مين اكتر 0000 protonated اكتر. 00000

$$pKa - pH = \log \frac{[protonated]}{[unprotonated]}$$

$$4 - 2 = \log \frac{[protonated]}{[unp.]}$$

$$\log \frac{[prot.]}{[unprot.]} = 2$$

ايه الرقم اللى ال log بتاعه بـ 2؟!
= 100

- $pKa - pH = \log \dfrac{Prot. [unIoni.]}{un \text{''} [Ioni]}$

- $4 - 2 = \log \dfrac{Pro[unIoni.]}{unpro[Ioni.]}$

- $2 = \log \dfrac{[pro]}{[unpro]}$

$$100 = \frac{Pro[unIoni.]}{unpro[Ioni.]}$$

∵ Un Ionized = 100 Ionized

∴ better absorption

$$\frac{[protonated]}{[unprotonated]} = 100$$

$$[protonated] = 100 [unprotonated]$$

يبقى كمية الـ protonated الموجودة اد 100 مرة الـ unprot. الـ

and as aspirin is weak acid

∴ protonated = unionized

↓ ∴ more lipophilic

∴ better absorption .

* يا رب يكله يكون فهم كنه ٠٠٠ لو فى حد لسة مش فاهم ، يبقى اشرحوله بس مهم اوى نكون فاهمين الكلام ده ٠٠٠

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* Problem :

انا لو عندى دواء عايزه يشتغل فى الـ kidney واحنا عارفين الـ pH بتاعة الـ urine بـ 8 ٠٠٠ معنى ان عايزه يشتغل فى الـ kidney يبقى مش عايز يحصله reabsorption فى الـ renal tubules

* Will I use urine acidifying drugs or alkalinizing drug ?!

اوعوا تتخضوا ٠٠٠ هى فكرتها سهلة اوى وئى اللى فوم

تعالوا نشوف هنعملها ازاى !؟

هنجرب الاول الـ urine acidifier ولنفرض الـ   pKa = 4

in Case of using Acidifying drugs

$$\log \frac{[\text{prot.}]}{[\text{unprot.}]} = pKa - pH$$

$$= 4 - 8$$
$$= -4$$

$$\therefore pKa - pH = \log \frac{\text{pro.}}{\text{unpro.}}$$

$$8 - 4 = \log \frac{\text{pro.}}{\text{unpro.}}$$

$$4 = \log \frac{\text{unpro.}}{\text{pro.}}$$

نقلبها while نشيل الـ ve-

$$\log \frac{[\text{unprot.}]}{[\text{prot.}]} = 4$$

$$\frac{[\text{unprot.}]}{[\text{prot.}]} = 10^4$$

$$\therefore [\text{unprot.}] = 10^4 [\text{prot.}]$$

i.e. unprotonated > protonated

And this case is weak acid
↓
i.e. protonated = unionized.
↓
i.e. ionized > unionized

& ionized is poorly absorbed

وهو الذي الاختيار اعمله ٥٥٥

$$\frac{\text{unpro.}}{\text{pro.}} = 10^4$$

$$\text{unpro.} = 10^4 \text{ pro}$$

$$\therefore \text{unpro.} > \text{pro.}$$

$$\therefore \text{Ionized} > \text{unIonized}$$

$$\therefore \downarrow \text{absorption}$$

∴ We use acidic drug
To acidifying ↓ urine
and Trap b Drug

∴ We Use weak acidic drug to acidify urine
and trap the drug (for ex: high dose of basic drugs)

N.B: Although Aspirin is an acidic drug (should be better absorbed from stomach) → it is absorbed more from the intestine due to high surface area of microvilli

---

°°° Absorption الـ بتاع الحـــوان قٓتٓ لسة نٓ ن مٓا احنا
°°° وٓ مٓزيد نٓقٓه فٓيه هٓنٓشٓوف

Factors Affecting Absorption

* 75% of the drugs taken orally are absorbed within 1→3 hours.

1) Blood Flow to the Absorption site:
blood flow in the intestine is greater than the stomach
∴ Absorption at the intestine is better.

2) Total Surface area available for absorption:

we mentioned before that the SA of intestine is very high (about 1000 times that of the stomach due to microvilli)

∴ Absorption across the intestine is more efficient.

3) Contact time at the absorption site:

- Better absorption takes place in empty stomach with faster gastric emptying.

- Presence of food in the stomach → dilutes the drug & slows gastric emptying

- In case of severe diarrhae (the drug moves through GIT very rapidly) → not well absorbed.

- Anything that delay transport of drug from stomach to the intestine → delays rate of drug absorption.

4) Physicochemical factors:

eg: - liberation from formula
- chelation
- pka
- solubility, ____ etc.

فى تجربينـا كده بس الدكتـور ما قلهمشى فى المحاضـرة ٠٠٠
اعرفـــوهم ٠٠٠ هما سهلـين ٠٠٠

* **Bioavailability:** It is the fraction of unchanged drug that gains access to the systemic circulation after administration by any route, eg: oral.

systemic circulation يعني بيسبقها كمية الدواء اللي هتوصل لل نظـل تنزل تأنيـل

✦ Bioavailability
↘ systemic circulation

by Ⅰ ✦ absorp^k
Ⅱ 1st Pass effect

oral Antibiotic 100mg in blood 1mg
→ IV " 1mg
-25- So 100mg at. is Bioequivalente to
1mg I-V

* <mark>Bioequivalence</mark> : <mark>Implies that if one formulation of a</mark> drug is substituted for another , No clinically untoward consequences will result.

يعنى لو بدلت الدواء بتاعى بدواء تانى ← يدينى نفس التأثير بالمنبط

ـــ

absorption احنا كـــــل ده كنا بنتكلم عن الـ pharmacokinetics اللى هى اول واحدة فى الـ (ADME) بتاعة الـ فاكـــرين ؟!! (look p. 15)

تعالـــوا نشـوف تانى حرف الـ D oooo

2 DISTRIBUTION

* <mark>Definition</mark> : <mark>The process by which a drug reversibly leaves the blood stream and enters the interstitial (extra cellular) fluid and/or cells of the tissue</mark>

يعنى فى الـ absorption الدواء عدى من المكان اللى اديته فيه للدم نكـــن فى الـ distribution هيـتوزع بقى من الدم للخلايا علشام يدينى التـــأثير المطلوب

* <mark>Factors affecting delivery of a drug from the plasma:</mark>

(Factors aff. distribution of drug)

A <u>Blood flow</u> : اكبر المكان اللى فيه blood flow عالى هيتوزع الدواء فيه اسهل واسرع.

<mark>blood flow to brain, liver & kidney > muscles & fat.</mark>

B Capillary Permeability: determined by:

1 Capillary structure:

eg: BBB (Blood Brain Barrier) where capillaries are continous with tight intercellular junctions

زي ما اخذنا في الـ Biopharmaceutics ان المخ خلاياه مقفولة بالـ tight junctions دى علشان مفيش حاجة غريبة تقدر توصل لـ CNS

∵ Only lipid soluble drugs can cross it, while polar drugs cannot.

• Drugs can also pass through "Active Transport".

• In contrast to that, are capillaries of liver & spleen.

2 Drug structure:

• Lipid soluble (Hydrophobic) drugs can readily pass through the membrane
While hydrophilic drugs, polar, with non uniform electron distribution → can't cross the membrane & pass through slit junction

خذنا في الـ Bio برده ك ده عبارة عن فتحة صغيرة في الخلية يقس منها السواء ليخش لداخل الخلية.

Lipid

C Binding to plasma proteins:

انا عايز الدواء يروح من ال plasma للخلايا ، فلو هو جه مسكن فى ال proteins الموجودة فى ال plasma > يبقى هيصعب خروجه للخلايا .

i.e. binding to plasma proteins ⟶ ↓ diffusion of drugs from plasma .

———————————

طيب نقولوا نشوف حاجة جديدة ودى فضلكم فتحوا متكـف محايا أوى فى النكتة دى علشان نفهمها كويس وانا هتناول ابسط الدنيا على قد ماقدر ٥٥٥٥

** Apparent Volume of Distribution (Vd) : **

هكتب ال def. كله حتة واحدة وبعدين هشـرحه

* def: It is the volume of plasma that would contain total body content of a drug at a concentration equal to that in the plasma !

* يعنى ايه القرف ده !؟ نشـرح نشـوية عرب الاول لازم نعرف أن ال Vd ده حاجة تخيلية او افتراضية hypothesis علشان تحدد لى اذا كان الدواء اللى اخدته وصل للمكان اللى انا عايزه فى الجسم وبال conc. اللى هتديني ال effect ولا ' لا ' ، رح العلم ان الدواء لما بيتاخد بيتوزع فى حتت كتـيرة اوى فى الجسم هنفرغا بعد نشوية من ضمنها المكان اللى هيدى فيه ال effect .

* Following absorption into the blood stream, a drug distributes into interstitial & intracellular fluid.

* طيب انا لازم الاقى الدواء (بعد ما يروح من حتت كتيرة فى الجسم)
بـ conc. معينة فى الـ plasma علشان يقدر يدينى التأثير المطلوب

يعنى لو واخدتا دواء 500mg ولما جيت اقيس كميته فى الـ plasma
لقيتها 0.1mg لكن وانا عارفة انه علشان يدى تأثير لازم تكون الـ conc.
اللى فى الـ plasma = 0.5mg ، يبقى انا لازم ادينله جرعة اكبر من
الدواء دى ٥ ٥ ٥

$$Vd = \frac{D}{C} \qquad or \qquad C = \frac{D}{Vd}$$

Volume of distribution
(constant parameter
of each drug)

Dose (total amount of
drug in the body)

conc. of drug in the plasma.

* كل ماال value بتاعتا الـ Vd بتزيد ⟶ ده معناه ان الدواء
استونج فى حتت كتيرة اوى فى الجسم وكميته فى الـ plasma قليلة اوى

* طيب انا ازاى هاستخدم دى فى الـ وايح علشان احد كمية الدواء
اللى احنه ويبقى الـ effect المطلوب ..

. we said that Vd ⟶ is constant for each drug.
- i'll give certain dose of the drug & measure its conc in
the plasma ⟶ C_1 (initial conc. in the plasma)
∴ Vd. C_1 = amount of drug initially in body.

. the conc. I need to find in the plasma = C_2
ودى انا عارفاها برضه
∴ Vd. C_2 = amount of drug in body needed to achieve the
desired plasma conc.
هو ده اللى انا عايزه .

• The diff. bet. the 2 values = $V_d.C_2 - V_d.C_1 = V_d(C_2-C_1)$

is the additional dosage needed

الكمية
وهى دى* اللى انا هاديها للمريض زيادة على الجرعة اللى بياخدها علشان~
اوصل لل. conc. اللى انا عايزاها فى الـ plasma (C_2) علشان~ اوصل للتأثير
المطلوب .

وصلت !!؟
يارب ٠٠٠
لو لسة موصلتش ٠٠ تعالوا اشرحهالكم ٠٠٠

═══════════════════

* طيب احنا قلنا ان الدواء هيتوزع فى اماكن كتيرة فى الجسم
ايه هى الاماكن دى؟٠٠٠٠
المكان الاول والى لازم يكون فى الدواء حتى لو بنسبة صغيرة
هــوال plasma ٠٠٠ وكل ده بيتحدد حسب الـ structure بتاعت الدواء

⁓⁓⁓ (Water Compartments in the body & drug distribution) ⁓⁓⁓

1) Plasma Compartments   كل الادوية لازم توصل لل. plasma

* if a drug has a very large M.wt
               or
binds extensively to plasma proteins ⟶ thus is trapped within
the plasma .

* (example) of drugs found only in plasma ፥ Insulin , Heparin

─────────────────

2) **Extracellular Fluid:**
   (Interstitial fluid)

في اختلافها دى الأدوية ٥
plasma + extracellular fluid

* drugs have low M.wt but hydrophilic ⟶ ٥٥ they can move through the endothelial slit junctions of capillaries into the interstitial fluids but can't cross the membranes of the cells.

* (Examples:) Tubocurarine , Theophylline

---

3) **Total Body Water:**

٥٥ هيعمل كله فيلاقيه في ٥
plasma + extracellular fluid + Intracellular
fluid ⟶ بس هيعمل يجدى من
كل حاجة وبدخل جوه الخلية

* if the drug has low M.wt and lipophilic ⟶ ٥٥ it can move also intracellularly into the cell.

(Example:) Ethanol, phenytoin & Paracetamol.

لو حب سؤال كده على الناس 000 ياترى هيجى من ال 3 Compartments اللي قلناهم فوق دول هيبقى عنده انا على Vd اى؟
فكروا شوية كده 0000 ٥
انا ممكن اساعدكم واقولكم ان ال Vd هى كمية الدواء للموزع من الجسم كمته من ال plasma divided by 000
ها عرفتوا اى؟
طلما ال total body water هيبقى على ال Vd لا انه اكبر من واحدة متوزعة من الجسم.

$$Vd = \frac{\text{Amt. of Drug distributed on body}}{\text{"   "   "   " in plasma}}$$

Page ③ ↝ هناك سؤال مهم وجاء في الإمتحانات
و لو فاهم الحتة بتاعت الـ Vd كويس هتحله ببساطة.

↝ if you have 2 cases of drug toxicity :
1ˢᵗ Case ↝ Toxicity with drug having high $\overline{V}d$
2ⁿᵈ " ↝ " " " " " Low $\overline{V}d$

↝ which one can be treated easier by blood
dialysis (غسيل الدم) ?

يعني أنا لو غسلت دم الإتنين هـ ميه اللي هيتعالج ؟

(Answer) : Surely : The one with to Low Vd will
be treated easier by dialysis
Because ↝ in case of drug with Low $\overline{V}d$ ↝ the drug
is more concentrated in plasma
∴ by plasma dialysis ↝ we get rid a great
amt. of the drug ↝ treating the toxicity
easily.

But ↝ in case of drug with ↑ Vd ↝ the drug is
distributed in different body compartments ↝ not
only plasma
∴ by plasma dialysis ↝ we get rid of a small
amt of the drug ↝ so small effect on treating
toxicity

لو موصلتش هـ تعالوا و احنا نفهمها لكم .

(N.B:)

Binding of drug outside the plasma compartment

or

Partitioning into body fat   يعني الدواء يروح لل fat اللى فى الجسم

$$\downarrow \quad Vd \text{ of fat} > Vd \text{ body water}$$

↑ Vd beyond total body water

وده طبعاً منطقى جداً لان الدواء مش هيتوزع بس على ال fluids
اللى فى الجسم لكن كمان ان شوية هيروحوا يتخزنوا
فى ال fat اللى فى الجسم

يبقى طبيعى ان ال Vd تزيد اوى وتبقى اعلى
من ال total body water

* (Examples) of drugs undergoing this mechanism :

digoxin, morphine, tricyclic antidepressant.

نبى خلاص :: خلصنا الجزء الفظيع ده ::

ومع آخر حاجة فى المحاضرة العظيمة دى o o o o

Plasma Protein Binding

* Drug molecules may bind to plasma proteins usually albumin.

| Bound Form ⇌ Free Form. |

pharmacologically inactive

only free drug can act on target sites in tissues, produce response

* The Binding to albumin is (reversible) with varying affinities , may show low or high capacity

يعني قابلية الدواء علشان عليك منه

(n° of drug molecules binding to single albumin molecule)

* Albumin has strongest affinity for anionic drugs (weak acids) & hydrophobic drugs

* الدكتور وقف هنا وهنكمل الموضوع ده المحاضرة الجاية.
* معلش ه المحاضرة طويلة شوية بس مش بإيدينا.

The Last & most imp. request o o o o
pLz o o o Pray 4 us a lot o o o.

Plasma Protein Binding ← في آخر صفحة في المحاضرة الثانية
(PPB)
← هنزود بعض الكلام في السريع كده .

Drug in plasma : ⟶ Bound to plasma proteins
∴ indiffusable ⟶ ∴ inactive.
⟶ Free drug in plasma
∴ diffusable ⟶ so active

⟶ The most Famous protein in plasma is { Albumin }

⟶ Albumin has 2 sites : ⟶ ① for acidic drugs
* has Low capacity But high affinity.

⟶ ② for Basic drugs
* has high capacity But Low affinity.

Drugs

class I	class II
effective when free in small percent	effective only when ↑ percent is free
1% for example	40% for example.
• free drug 1%	bound drug 60% free drug 40%
bound drug 99%	
example : tolbutomide drug	example : Sulfonamide
for insuline release, glucose regulatn,	

→ class I drugs → if displacement interaction occurs another percent of bound drug becomes free giving a toxic effect

يعنى إيه؟

هو يعنى لو أى drug له affinity لل plasma proteins أكتر من ال drug اللى أصلاً ماسك → هيدخل مكانه ويعمل release لل drug اللى هو كان effective بـ (small percent (1%) فال free percent هتزيد تبقى مثلاً 2% هو كده يبقى ضاعفنا ال dose و بقى ال drug → Toxic.

∴ displacement interaction here is dangerous.

→ Danger of displacement interaction :
① decreases as | Therapeutic index increases. | LI↑
② " " as | V_d ↑ " |

كن مع المحاضرة الثانية تبقى تمام .

```
┌─────────────────────────┐
│  Lecture ③   زيادات على  │
└─────────────────────────┘
```

. هنرسم رسمة علشان نوضح تحول ال drugs لل metabolism معلكم يكون عامل إزاى

Lipophilic drug. ──────→ ┌──────┐ ──→ hydrophilic drug
active drug ──────→ │ Liver │ ──→ inactive drug.
active drug ──────→ │   │ ──→ more active drug (morphine)
    (codein)   │   │
inactive drug (prodrug) ──→ └──────┘ ──→ active drug.
    (Metronidazole)
active drug ──────────────────→ toxic metabolites.
    (Paracetamol)